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The Patent Office
Cardiff Road
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1. Your reference — MG/PMS/P33134

2. Patent application number
(The Patent Office will fill in his part) — 0225678.2 — -4 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 4735870003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectu

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

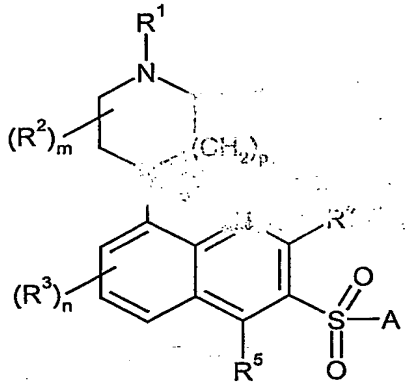
P33134

NOVEL COMPOUNDS

This invention relates to novel quinoline compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081 discloses a series of aryl sulphonamide compounds that are said to be 5-HT_6 receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. GB-2341549, WO 99/47516 and WO 99/65906 all disclose a series of indole derivatives that are claimed to 5-HT_6 receptor affinity. JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements. WO 00/42026 (Novo Nordisk) describes a series of quinoline and quinoxaline compounds for use as GLP-1 agonists.

A structurally novel class of compounds has now been found which also possess affinity for the 5-HT_6 receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

R^3, R^4 and R^5 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^6R^7$;

R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

m represents an integer from 1 to 4, when m is an integer greater than 1, two R^2 groups may instead be linked to form a group CH_2, $(CH_2)_2$ or $(CH_2)_3$;

n represents an integer from 1 to 3;

p represents 1 or 2;

A represents a group $-Ar^1$ or $-Ar^2Ar^3$;

Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^8R^9$ or $SO_2NR^8R^9$, wherein R^8 and R^9 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

Preferably, R^1 represents hydrogen or methyl. More preferably, R^1 represents hydrogen.
Preferably R^2 represents hydrogen or methyl (eg. 3-methyl). More preferably, R^2 represents hydrogen.
Preferably R^3 represents hydrogen, methyl (eg. 6-methyl) or halogen (eg. 7-chloro). More preferably, R^3 represents hydrogen.
Preferably R^4 and R^5 independently represent hydrogen or methyl, especially hydrogen.

Preferably m, n and p all represent 1.

When A represents a group $-Ar^1$, Ar^1 preferably represents optionally substituted phenyl or pyridyl, more preferably phenyl optionally substituted with halogen (eg. chlorine, fluorine or bromine), cyano, trifluoromethyl or trifluoromethoxy. Particularly preferred Ar^1 is unsubstituted phenyl or phenyl substituted by halogen (eg. 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 3-fluoro or 4-bromo), trifluoromethyl (eg. 3-trifluoromethyl) or trifluoromethoxy (eg. 2-trifluoromethoxy).

When A represents a group $-Ar^2-Ar^3$, Ar^2 and Ar^3 preferably both independently represent phenyl or monocyclic heteroaryl group as defined above.

Preferably A represents a group $-Ar^1$.

Most preferred $-Ar^1$ is unsubstituted phenyl.

Preferred compounds according to the invention include examples E1-E15 as shown below, or a pharmaceutically acceptable salt thereof.

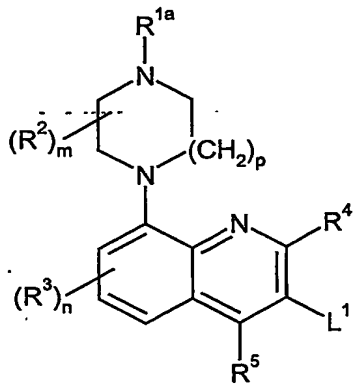
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

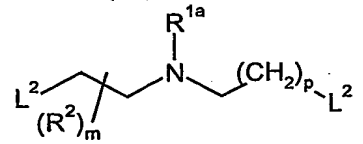
wherein R^{1a} is as defined for R^1 or an *N*-protecting group, R^2, R^3, R^4, R^5, m, n and p are as defined above and L^1 is a leaving group such as iodo or trifluoromethylsulfonyloxy;
with a compound of formula A-SO_2H, (or A-SH followed by a subsequent oxidation step) wherein A is as defined above and thereafter as necessary removing an R^{1a} *N*-protecting group;

(b) deprotecting a compound of formula (I) which is protected; and thereafter optionally

(c) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

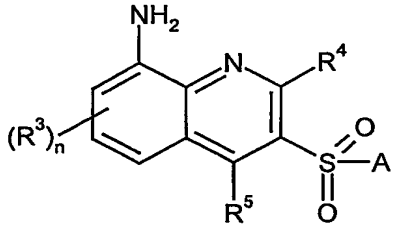
The present invention also provides a further process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(d) reacting a compound of formula (IV)



(IV)

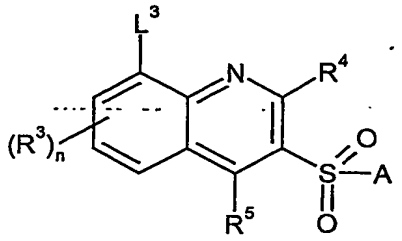
with a compound of formula (V)



(V)

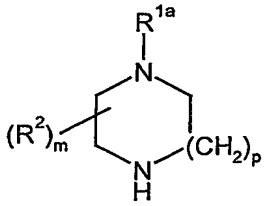
wherein R^{1a}, R^2, R^3, R^4, R^5, A, m, n and p are as defined above, and L^2 represents a suitable leaving group, such as a halogen atom and thereafter as necessary removing an R^{1a} *N*-protecting group; or

(e) reacting a compound of formula (VI)



(VI)

with a compound of formula (VII)



(VII)

wherein R^{1a}, R^2, R^3, R^4, R^5, m, n, p and A are as defined above and L^3 represents a suitable leaving group, such as a halogen atom (eg. a bromine or iodine atom) or a trifluoromethylsulfonyloxy group, and thereafter as necessary removing an R^{1a} *N*-protecting group.

The *N*-protecting group used may be any conventional group e.g. t-butyloxycarbonyl (Boc) or benzyloxycarbonyl. A further *N*-protecting group which may be used includes methyl.

Process (a) wherein a compound of formula (II) is reacted with a compound of formula A-SO_2H typically comprises use of basic conditions and may be most conveniently carried out by using a suitable salt of the compound A-SO_2H (e.g. the sodium salt) in an appropriate solvent such as *N,N*-dimethylformamide, in the presence of a transition metal salt such as copper (I) iodide.

Process (a) wherein a compound of formula (II) is reacted with a compound of formula A-SH typically comprises use of basic conditions e.g. by using a suitable salt of the compound A-SH (e.g. the sodium salt) in an appropriate solvent such as *N,N*-dimethylformamide, in the presence of a suitable metal salt such as copper (I) iodide, followed by use of a suitable oxidant such as 3-chloroperbenzoic acid, peracetic acid or potassium monopersulfate.

In processes (a) and (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase

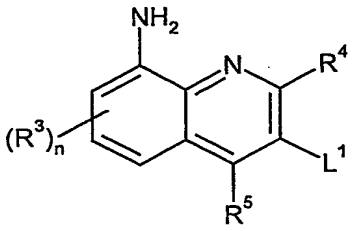
resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid. A further amine protecting group includes methyl which may be removed using standard methods for N-dealkylation (e.g. 1-chloroethyl chloroformate under basic conditions followed by treatment with methanol).

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, *N*-dealkylation of a compound of formula (I) wherein R^1 represents an alkyl group to give a compound of formula (I) wherein R^1 represents hydrogen. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion.

Process (d) may be performed in the presence of a suitable base, such as sodium carbonate and the use of a suitable solvent such as *n*-butanol.

Process (e) may be performed in the presence of a palladium, nickel or copper catalyst, for example a mixture of a palladium source such as $Pd_2(dba)_3$ and a suitable ligand such as (R)-, (S)- or (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or (2-dicyclohexylphosphinophenyl)dimethylamine, together with a suitable base such as sodium *t*-butoxide, in an inert solvent such as 1,4-dioxane.

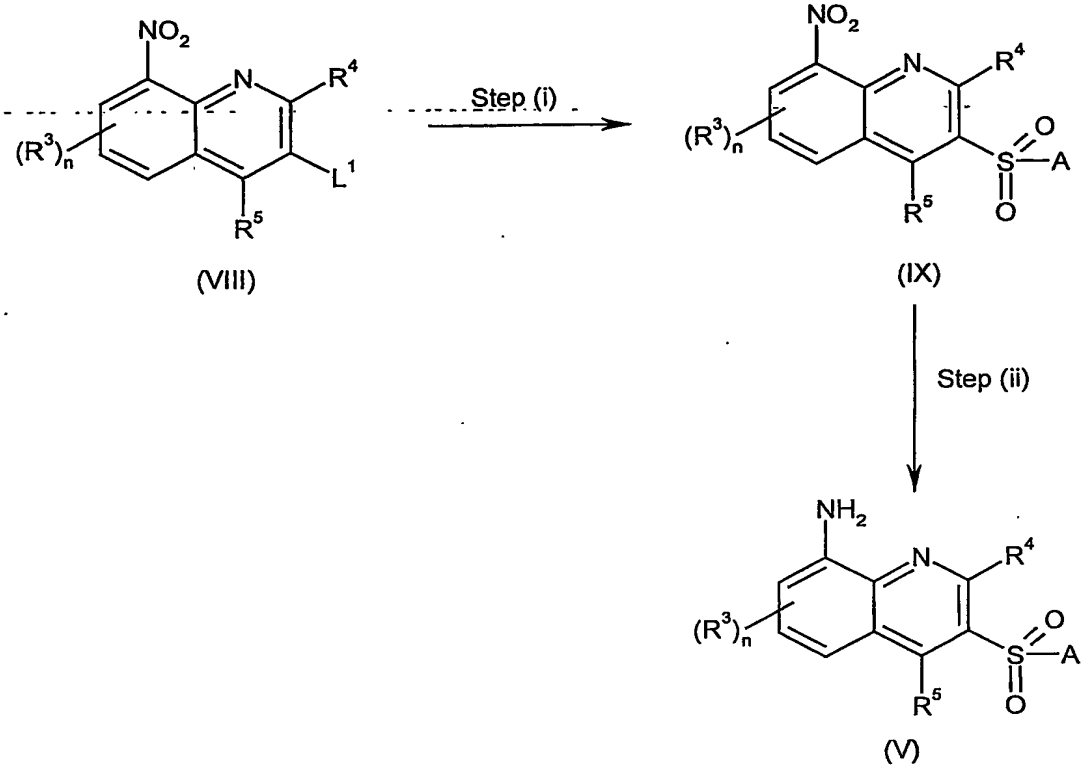
Compounds of formula (I) may be prepared by reacting a compound of formula (III)



(III)

wherein R^3, R^4, R^5, n and L^1 are as defined above, with a compound of formula (IV) as defined above. This process typically comprises the use of a suitable base, such as sodium carbonate and the use of a suitable solvent such as *n*-butanol.

Compounds of formula (V) may be prepared in accordance with the following scheme:



wherein R^3, R^4, R^5, n, A and L^1 are as defined above.

Step (i) typically comprises reaction of a compound of formula (VIII) with a compound of formula A-SO_2-M, wherein A is as defined above and M is a metal residue such as sodium or potassium, in the presence of a copper (I) salt, e.g. copper (I) triflate, in a suitable solvent such as anhydrous *N,N*-dimethylformamide. Step (i) may also typically comprise reaction of a compound of formula (VIII) with a compound of formula A-SH in the presence of a base such as sodium hydride in a suitable solvent such as anhydrous *N,N*-dimethylformamide, followed by an oxidation step using a suitable oxidant such as 3-chloroperbenzoic acid, peracetic acid or potassium monopersulfate.

Step (ii) typically comprises the use of a suitable reducing agent, for example titanium (III) chloride, in an appropriate solvent system, e.g. aqueous tetrahydrofuran.

Compounds of formula (VI) wherein L^3 represents a halogen atom may be prepared from compounds of formula (V) as defined above, by diazotisation according to known methods, followed by treatment of the resulting diazonium salt with an appropriate halide salt such as copper (I) bromide, potassium iodide or tetrabutylammonium iodide. Such a procedure may be carried out in aqueous solution or using anhydrous conditions, for example using trifluoroacetic acid as solvent.

Compounds of formula (VI) wherein L^3 represents a trifluoromethylsulfonyloxy group may be prepared from compounds of formula (V) as defined above, by diazotisation according to known

methods, followed by heating under acidic conditions, followed by treatment with trifluoromethylsulfonic anhydride in the presence of a base, such as pyridine.

Compounds of formula (III), (IV), (VII) and (VIII) are known in the literature or can be prepared by analogous methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT_6 receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, obesity and cognitive memory disorders

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations,

powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

3-Bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1)

bis-(2-Chloro-ethyl)-amine hydrochloride (3.7g, 19.2mmol) and sodium carbonate (9.0g, 85mmol) were added to a suspension of 3-bromo-quinolin-8-ylamine (3.9g, 17.5mmol) (for synthesis see Gershon *et al.*, *Monatsh. Chem.*, 1991, **122**, 935) in *n*-butanol (70ml). The stirred suspension was heated at reflux for 72h. The reaction mixture was cooled to ambient temperature, diluted with dichloromethane (300ml) and the solution washed with water (300ml), dried ($MgSO_4$) and concentrated *in vacuo* to an oil. The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane to afford the title compound (D1) as an oil (2.6g, 8.5mmol, 49%).

δ_H ($CDCl_3$) 2.43 (3H, s), 2.78 (4H, br s), 3.44 (4H, br, s), 7.14 (1H, d, J = 6.8Hz), 7.33 (1H, d, J = 7.4Hz), 7.47 (1H, dd, J = 7.8Hz), 8.25 (1H, d, J = 2.3Hz), 8.85 (1H, d, J = 2.3Hz).

Mass Spectrum : $C_{14}H_{16}BrN_3$ requires 305/307; found 306/308 (MH^+).

Description 2

3-Iodo-8-(4-methyl-piperazin-1-yl)-quinoline (D2)

A mixture of 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1)(1.75g, 5.7mmol), copper (I) iodide (5.4g, 28.5mmol) and potassium iodide (9.6g, 57.8mmol) in hexamethylphosphoramide (20ml) was heated in an oil bath at 150°C for 21h under argon. To the cooled reaction mixture was added toluene (100ml) and 2M hydrochloric acid (120ml) and the whole was shaken vigorously for 5 minutes. The insoluble brown solid was then collected by filtration, washed with methanol (3 x 40ml) and resuspended in a mixture of dichloromethane (150ml) and 2M sodium hydroxide (150ml). After shaking the mixture vigorously, the insoluble material was filtered, washed with dichloromethane (2 x 50ml) and discarded. The filtrate and washings were transferred to a separating funnel and the layers were separated. The aqueous phase was extracted with dichloromethane (2 x 100ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated to a brown oil (1.5g) which was identified by NMR spectroscopy as a mixture of the title compound (D2) and 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1) in a ratio of 4:1. This mixture was used directly in the next stage (see Example 1).

3-Iodo-8-(4-methyl-piperazin-1-yl)-quinoline (D2): δ_H ($CDCl_3$) 2.41 (3H, s), 2.76 (4H, br s), 3.42 (4H, br s), 7.14 (1H, d, J = 6.8Hz), 7.29 (1H, d, J = 7.4Hz), 7.44 (1H, dd, J = 7.8Hz), 8.47 (1H, d, J = 2.3Hz), 8.98 (1H, d, J = 2.3Hz).

Mass Spectrum : $C_{14}H_{16}IN_3$ requires 353; found 354 (MH^+).

Description 3

3-Iodo-8-nitroquinoline (D3)

A stirred mixture of 8-nitroquinoline (100 g, 0.57 mol) in acetic acid (500 ml) was treated with *N*-iodosuccinimide (155 g, 0.69 mol) portionwise over 10 minutes, and warmed to 62 °C for 6 h. A further portion of *N*-iodosuccinimide (25 g, 0.14 mol) was introduced and the mixture stirred for a further 16 h before cooling to ambient temperature. The solvent was removed *in vacuo*,

keeping the temperature below 35 °C. The residue was dissolved in dichloromethane (2 L) and washed successively with saturated aqueous sodium bicarbonate solution (2 x 1 L), 10% aqueous sodium thiosulphate solution (1 L), water (1 L), brine (100 ml), then the organic phase was dried over magnesium sulphate. The mixture was filtered and the solvent removed to give a yellow solid which was recrystallised from ethyl acetate to give the title compound (D3) (168 g, 97%) as a yellow solid.

δ_H ($CDCl_3$) 7.65 (1H, app.t), 7.94 (1H, dd), 8.07 (1H, dd), 8.66 (1H, d, J = 2Hz), 9.19 (1H, d, J = 2Hz);

Mass Spectrum : $C_9H_5IN_2$ requires 300; found 301 (MH^+).

Description 4

8-Nitro-3-phenylsulfonylquinoline (D4)

3-Iodo-8-nitroquinoline (D3) (135 g, 0.45 mol), was suspended in dimethylformamide (2.4 L) in a 5 L 3-necked flask fitted with an overhead stirrer, under an argon atmosphere. This mixture was treated successively with anhydrous sodium phenylsulfinate (99.6 g 0.608 mol), and bis-(copper (I) triflate) benzene complex (170 g, 0.338 mol). The resulting slurry was heated to 65 °C for 18 h. The mixture was cooled, filtered and the solvent evaporated *in vacuo*. Acetone (2.5 L) was added to the residue and the solution filtered. The filtrate was evaporated *in vacuo*, a further 2.5 L of acetone added and the mixture filtered again. The solvent was evaporated *in vacuo* and the residue dissolved in chloroform (3 L) and washed with 10% aqueous ammonia (2 x 2 L), and the organic phase was dried over magnesium sulphate and the solvent evaporated *in vacuo*. The dark brown residue was purified using a Biotage flash-150 chromatography [illegible] (5 kg silica gel) eluting with hexane and increasing proportions of ethyl acetate to give the title compound (D4) (81.5 g, 58%) as a yellow solid;

δ_H ($CDCl_3$) 7.53-7.64 (3H, m), 7.19 (1H, t), 8.03 (3h, dd), 8.17-8.23 (2H, m), 8.95 (1H, d), 9.38 (1H, d);

Mass Spectrum : $C_{15}H_{10}SO_4N_2$ requires 314; found 315 (MH^+).

Description 5

8-Amino-3-phenylsulfonylquinoline (D5)

A slurry of 8-nitro-3-phenylsulfonylquinoline (D4) (46.7 g, 172 mmol), in tetrahydrofuran (750 ml) was added to a stirred solution of 30% titanium (III) chloride in aqueous HCl (470 ml) [Supplied by BDH] cooled in an ice bath, at such a rate that the temperature was maintained below 35°C. Once the addition was completed, the solution was stirred for a further 10 minutes then water (1.5 L) was introduced and the mixture poured into a 5 L beaker. The rapidly stirred solution was treated by portionwise addition of solid potassium carbonate in order to attain pH ~8.5. EDTA (250 g, 0.86 mol) was added and followed by further potassium carbonate to maintain pH ~8.5. The mixture was extracted with dichloromethane (3 x 1 L) and the combined organic phase passed through a silica plug (500 g) eluting with further dichloromethane (1 L) and 10% ethyl acetate in dichloromethane (1 L). The combined organic phases were evaporated and the residue subjected to purification using Biotage Flash-75 chromatography apparatus (2 kg silica gel), eluting with dichloromethane and increasing proportions of ether to give the title compound (D5) (34.5 g, 72%) as a pale brown solid;

δ_H ($CDCl_3$) 5.0 (2H, br s), 7.02 (1H, dd), 7.25 (1H, dd), 7.44 (1H, t), 7.50-7.59 (3H, m), 8.00-8.40 (2H, m), 8.70 (1H, s), 0.09 (1H, s);
Mass Spectrum : $C_{15}H_{12}SO_2N_2$ requires 284; found 285 (MH^+).

Description 6

8-Iodo-3-phenylsulfonylquinoline (D6)

8-Amino-3-phenylsulfonylquinoline (D5) (31.6 g, 0.11 mol) was dissolved in trifluoroacetic acid (60 ml) and the mixture evaporated. The resulting brown oil was dissolved in acetonitrile (200 ml) and added dropwise to a stirred solution of *n*-butyl nitrite (6.1 ml) in acetonitrile (300 ml) maintained at a temperature of <5 °C. Once the addition was completed, the mixture was stirred for five minutes then tetra-(*n*-butyl)ammonium iodide (82 g, 0.22 mol) added portionwise, keeping the temperature below 10 °C. The mixture was stirred for a further 20 minutes then concentrated *in vacuo*. The dark residue was subjected to flash-75 chromatography (2 kg silica gel), eluting with hexane and dichloromethane to give a brown solid. This was dissolved in dichloromethane (500 ml) and washed with 10% aqueous sodium thiosulphate (2 x 300 ml), dried over magnesium sulphate and concentrated to an orange solid. This was triturated with methanol to give the title compound (D6) (25.2 g, 75%) as a light yellow solid;
δ_H ($CDCl_3$) 7.39 (1H, t), 7.53-7.63 (3H, m), 7.96 (1H, d), 8.04 (2H, dd), 8.50 (1H, dd), 8.79 (1H, d), 9.32 (1H, d);
Mass Spectrum : $C_{15}H_{10}NO_2SI$ requires 395; found 396 (MH^+).

Description 7

8-(4-*t*-Butoxycarbonyl)piperazin-1-yl-3-phenylsulfonylquinoline (D7)

8-Iodo-3-phenylsulfonylquinoline (D6) (25.2 g, 63.6 mmol) was dissolved in dry, de-gassed dioxan (500 ml) under argon. To this solution was added sodium *t*-butoxide (8.56 g, 89.2 mmol) and 1-*t*-butyloxycarbonyl piperazine (14.2 g, 76.4 mmol) followed by a suspension of catalyst under argon. The catalyst was prepared by sonication of a mixture of *tris*-(dibenzylideneacetone)dipalladium(0) (1.75 g, 1.91 mmol) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethyl amino)biphenyl (2.25 g, 5.73 mmol) in dry degassed dioxane (10 ml) for 2 minutes. This mixture was stirred at 40 °C for 5 h after which a further charge of catalyst was administered (prepared as above on half the scale) and stirring continued for 16 h at 40 °C. The mixture was filtered and the solvent removed. The residue was adsorbed onto silica and chromatographed on silica eluting with 1% methanol in dichloromethane to give the title compound (D7) (22.0 g, 76%) as a yellow solid;
δ_H ($CDCl_3$) 1.49 (9H, t), 3.31 (4H, m) 3.72 (4H, m), 7.25 (1H, m), 7.52 (2H, t) 7.57 (3H, m) 8.00 (2H, m) 8.76 (1H, d) 9.21 (1H, d);
Mass Spectrum: $C_{24}H_{27}N_3O_4S$ requires 453; found 454 (MH^+).

Description 8

8-(4-*t*-Butoxycarbonyl)piperazin-1-yl-3-(3-trifluoromethyl)phenylsulfonylquinoline (D8)

This was prepared from 8-iodo-(3-trifluoromethyl)phenylsulfonylquinoline (D34) in an analogous process to that described in Description 7 (D7).

δ_H ($CDCl_3$)1.50 (9H, s), 3.32 (4H, t), 3.73 (4H, t), 7.28 (1H, d), 7.59 (1H, s), 7.61 (1H, d), 7.69 (1H, t), 7.85 (1H, d), 8.21 (1H, d), 8.28 (1H, s), 8.79 (1H, d), 9.23 (1H, s).
Mass Spectrum: $C_{25}H_{26}F_3N_3O_4S$ requires 521; found 522 (MH^+).

Description 9

8-(4-*t*-Butoxycarbonyl)homopiperazin-1-yl-3-phenylsulfonylquinoline (D9)

Prepared using an analogous process to that described in Description 7 (D7), using 8-iodo-3-phenylsulfonylquinoline (D6) (200 mg, 0.51 mmol), sodium *t*-butoxide (68 mg, 0.71 mmol), 1-(*t*-butyloxycarbonyl)homopiperazine (122 mg, 0.61 mmol), *tris*-(dibenzylideneacetone)dipalladium(0) (14 mg, 0.015 mmol) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethyl amino)biphenyl (18 mg, 0.045 mmol). This resulted in the formation of a mixture containing the title compound (D9). The mixture was cooled, filtered, the solvent evaporated and the crude material was used directly in Example 14 (E14).
Mass Spectrum: $C_{25}H_{29}N_3O_4S$ requires: 467 found: 468 (MH^+)

Description 10

8-Amino-3-(2-chloro)phenylsulfonylquinoline (D10)

Prepared from 3-(2-chloro)phenylsulfonyl-8-nitro-quinoline (D18) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.0 (2H, br s), 7.07 (1H, d), 7.27 (1H, d), 7.43-7.47 (2H, m), 7.52-7.57 (2H, m), 8.44-8.46 (1H, m), 8.77 (1H, d), 9.05 (1H, d);
Mass Spectrum : $C_{15}H_{11}ClN_2O_2S$ requires 318, 320; found 319, 321 (MH^+).

Description 11

8-Amino-3-(3-chloro)phenylsulfonylquinoline (D11)

Prepared from 3-(3-chloro)phenylsulfonyl-8-nitro-quinoline (D19) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.0 (2H, br s), 7.05 (1H, d), 7.27 (1H, d), 7.43-7.57 (3H, m), 7.89 (1H, d), 8.00 (1H, t), 8.70 (1H, d), 9.08 (1H, d);
$C_{15}H_{11}ClN_2O_2S$ requires 318, 320; found 319, 321 (MH^+).

Description 12

8-Amino-3-(2-fluoro)phenylsulfonylquinoline (D12)

Prepared from 3-(2-fluoro)phenylsulfonyl-8-nitro-quinoline (D20) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.1 (2H, br s), 7.08 (2H, t), 7.27 (1H, d), 7.36 (1H, t), 7.46 (1H, m), 7.55-7.63 (1H, m), 8.19 (1H, t), 8.79 (1H, t), 9.14 (1H, t);
Mass Spectrum : $C_{15}H_{11}FN_2O_2S$ requires 302; found 303 (MH^+).

Description 13

8-Amino-3-(4-chloro)phenylsulfonylquinoline (D13)

Prepared from 3-(4-chloro)phenylsulfonyl-8-nitro-quinoline (D21) in an analogous process to that described in Description 5 (D5).

δ_H ($CDCl_3$) 5.0 (2H, br s), 7.05 (1H, dd), 7.25 (1H, dd), 7.42-7.53 (3H, m), 7.95 (2H, dt), 8.68 (1H, d), 9.07 (1H, s);
Mass Spectrum : $C_{15}H_{11}N_2SO_2Cl$ requires 318, 320; found 319, 321 (MH^+).

Description 14

8-Amino-3-(3-fluoro)phenylsulfonylquinoline (D14)

Prepared from 3-(3-fluoro)phenylsulfonyl-8-nitro-quinoline (D22) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.0 (2H, br s), 7.05 (1H, dd), 7.24-7.29 (2H, m), 7.44 (1H, d), 7.52 (1H, dt), 7.72 (1H, dt), 7.82 (1H, dt), 8.70 (1H, d), 9.09 (1H, d);
Mass Spectrum : $C_{15}H_{11}N_2O_2SF$ requires 302; found 303 (MH^+).

Description 15

8-Amino-3-(4-bromo-2-trifluoromethoxy)phenylsulfonylquinoline (D15)

Prepared from 3-(4-bromo-2-trifluoromethoxy)phenyl-8-nitro-sulfonylquinoline (D23) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.0 (2H, br s), 7.07 (1H, dd), 7.26 (1H, dd), 7.43-7.48 (2H, m), 7.65 (1H, dd), 8.21 (1H, d), 8.72 (1H, d), 9.04 (1H, d);
Mass Spectrum : $C_{16}H_{10}N_2O_3SF_3Br$ requires 446, 448; found 447, 449 (MH^+).

Description 16

8-Amino-6-methyl-3-phenylsulfonylquinoline (D16)

Prepared from 6-methyl-8-nitro-3-phenylsulfonylquinoline (D24) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 2.45 (3H, s), 4.94 (2H, br s), 6.90 (1H, s), 7.04 (1H, s), 7.50-7.60 (3H, m), 8.02 (2H, d), 8.60 (1H, s), 9.01 (1H, s);
Mass Spectrum : $C_{16}H_{14}N_2O_2S$ requires 298; found 299 (MH^+).

Description 17

8-Amino-3-(3-trifluoromethyl)phenylsulfonylquinoline (D17)

Prepared from 8-nitro-3-(3-trifluoromethyl)phenylsulfonylquinoline (D25) in an analogous process to that described in Description 5 (D5).
δ_H ($CDCl_3$) 5.0 (2H, br s), 7.06 (1H, dd), 7.27 (1H, d), 7.47 (1H, t), 7.69 (1H, t), 7.85 (1H, d), 8.20 (1H, d), 8.29 (1H, s), 8.73 (1H, d), 9.10 (1H, d);
Mass Spectrum : $C_{16}H_{11}N_2O_2SF_3$ requires 352; found 353 (MH^+).

Description 18

3-(2-Chloro)phenylsulfonyl-8-nitro-quinoline (D18)

A mixture of 3-(2-chloro)phenylsulfanyl-8-nitro-quinoline (D26) (0.63 g, 2.0 mmol) and 3-chloroperbenzoic acid (1.73 g, 10 mmol) in dichloromethane (10 ml) was stirred at room temperature for 3 h. The mixture was then diluted with dichloromethane (50 ml) and washed with saturated aqueous sodium metabisulfite (50 ml), saturated aqueous sodium hydrogencarbonate

(50 ml), dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (D18) (0.65g, 94%) as an orange paste;
δ_H ($CDCl_3$) 7.06 (1H, d), 7.27 (1H, d), 7.44 (1H, s), 7.52-7.57 (3H, m), 8.48 (1H, d), 8.76 (1H, d), 9.05 (1H, d);
Mass Spectrum : $C_{15}H_9ClN_2O_4S$ requires 348, 350; found 349, 351 (MH^+).

Description 19
3-(3-Chloro)phenylsulfonyl-8-nitro-quinoline (D19)
Prepared from 3-(3-chloro)phenylsulfanyl-8-nitro-quinoline (D27) in an analogous process to that described in Description 18 (D18).
δ_H ($CDCl_3$) 7.52 (1H, t), 7.62 (1H, d), 7.81 (1H, t), 7.93 (1H, d), 8.00 (1H, s), 8.21-8.24 (2H, m), 8.95 (1H, d), 9.39 (1H, d);
Mass Spectrum : $C_{15}H_9ClN_2O_4S$ requires 348, 350; found 349, 351 (MH^+).

Description 20
3-(2-Fluoro)phenylsulfonyl-8-nitro-quinoline (D20)
Prepared from 3-(2-fluoro)phenylsulfanyl-8-nitro-quinoline (D28) in an analogous process to that described in Description 18 (D18).
δ_H ($CDCl_3$) 7.17 (1H, t), 7.40 (2H, t), 7.65 (1H, m), 7.81 (1H, t), 8.20-8.27 (2H, m), 9.05 (1H, t), 9.40 (1H, t);
Mass Spectrum : $C_{15}H_9FN_2O_4S$ requires 332; found 333 (MH^+).

Description 21
3-(4-Chloro)phenylsulfonyl-8-nitro-quinoline (D21)
Prepared from 3-(4-chloro)phenylsulfanyl-8-nitro-quinoline (D29) in an analogous process to that described in Description 18 (D18).
δ_H ($CDCl_3$) 7.54 (2H, dt), 7.80 (1H, t), 7.97 (2H, dt), 8.20 (2H, d), 8.92 (1H, d), 9.37 (1H, d);
Mass Spectrum : $C_{15}H_9N_2SO_4Cl$ requires 348, 350; found 349, 351 (MH^+).

Description 22
3-(3-Fluoro)phenylsulfonyl-8-nitro-quinoline (D22)
Prepared from 3-(3-fluoro)phenylsulfanyl-8-nitro-quinoline (D30) in an analogous process to that described in Description 18 (D18).
Mass Spectrum : $C_{15}H_9N_2O_4SF$ requires 332; found 333 (MH^+).

Description 23
3-(4-Bromo-2-trifluoromethoxy)phenyl-8-nitro-sulfonylquinoline (D23)
Prepared from 3-(4-bromo-2-trifluoromethoxy)phenyl-8-nitro-sulfanylquinoline (D31) in an analogous process to that described in Description 18 (D18).
Mass Spectrum : $C_{16}H_8N_2O_5SF_3Br$ requires 476, 478; found 479, 481 (MH^+).

Description 24
6-Methyl-8-nitro-3-phenylsulfonylquinoline (D24)

Prepared from 6-methyl-8-nitro-3-phenylsulfanylquinoline (D32) in an analogous process to that described in Description 18 (D18).

δ_H ($CDCl_3$) 2.65 (3H, s), 7.60-7.67 (3H, m), 7.95 (1H, s), 8.00-8.05 (3H, m), 8.82 (1H, d), 9.30 (1H, d);

Mass Spectrum : $C_{16}H_{12}N_2O_4S$ requires 328; found 329 (MH^+).

Description 25

8-Nitro-3-(3-trifluoromethyl)phenylsulfonylquinoline (D25)

Prepared from 8-nitro-3-(3-trifluoromethyl)phenylsulfanylquinoline (D33) in an analogous process to that described in Description 18 (D18).

δ_H ($CDCl_3$) 7.75 (1H, t), 7.82 (1H, t), 7.91 (1H, d), 8.22-8.25 (3H, m), 8.30 (1H, s), 8.98 (1H, d), 9.40 (1H, d);

Mass Spectrum : $C_{16}H_9N_2O_2SF_3$ requires 381; found 382 (MH^+).

Description 26

3-(2-Chloro)phenylsulfanyl-8-nitro-quinoline (D26)

To a suspension of sodium hydride (0.16 g, 6.67 mmol) in dimethylformamide (10 ml) was slowly added 2-chlorothiophenol (0.96 g, 6.67 mmol) as a solution in dimethylformamide (5 ml). The reaction mixture was stirred for 10 minutes, then a solution of 3-iodo-8-nitroquinoline (D3) (1.0 g, 3.33 mmol) in dimethylformamide (5 ml) was added slowly and the mixture heated to 90 °C for 4 hours. The mixture was cooled to ambient temperature, then water (50 ml) was added carefully and the mixture extracted with dichloromethane (2 x 50 ml). The organic phase was washed with brine (50 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by chromatography on silica, eluting with a hexane/ethyl acetate gradient to provide the title compound (D26) (0.70g, 70%) as a brown oil.

δ_H ($CDCl_3$) 7.25-7.28 (1H, m), 7.34 (1H, t), 7.40 (1H, d), 7.51 (1H, d), 7.63 (1H, t), 7.93 (1H, d), 8.02 (1H, d), 8.09 (1H, s), 8.87 (1H, s);

Mass Spectrum : $C_{15}H_9ClN_2O_2S$ requires 316, 318; found 317, 319 (MH^+).

Description 27

3-(3-Chloro)phenylsulfanyl-8-nitro-quinoline (D27)

Prepared from 3-iodo-8-nitroquinoline (D3) and 3-chlorothiophenol in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 7.35 (3H, br s), 7.45 (1H, s), 7.63 (1H, s), 7.92 (1H, s), 8.02 (1H, d), 8.10 (1H, s), 8.89 (1H, s);

Mass Spectrum : $C_{15}H_9ClN_2O_2S$ requires 316, 318; found 317, 319 (MH^+).

Description 28

3-(2-Fluoro)phenylsulfanyl-8-nitro-quinoline (D28)

Prepared from 3-iodo-8-nitroquinoline (D3) and 2-fluorothiophenol in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 7.21 (1H, d), 7.42-7.49 (2H, m), 7.53-7.62 (2H, m), 7.88 (1H, d), 7.97 (1H, d), 8.04 (1H, d), 8.86 (1H, d);

Mass Spectrum : $C_{15}H_9FN_2O_2S$ requires 300; found 301 (MH^+).

Description 29

3-(4-Chloro)phenylsulfanyl-8-nitro-quinoline (D29)

Prepared from 3-iodo-8-nitroquinoline (D3) and 4-chlorothiophenol in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 7.00 (1H, dd), 7.25-7.50 (3H, m), 7.56 (2H, d), 7.99 (1H, dd), 8.24 (1H, d), 8.81 (1H, d);

Mass Spectrum : $C_{15}H_9N_2O_2SCl$ requires 316, 318; found 317, 319 (MH^+).

Description 30

3-(3-Fluoro)phenylsulfanyl-8-nitro-quinoline (D30)

Prepared from 3-iodo-8-nitroquinoline (D3) and 3-fluorothiophenol in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 7.07 (1H, dt), 7.15 (1H, dt), 7.22 (1H, dt), 7.35 (1H, dd), 7.62 (1H, dd), 7.94 (1H, dd), 8.02 (1H, dd), 8.11, (1H, d), 8.89 (1H, d);

Mass Spectrum : $C_{15}H_9N_2SO_2F$ requires 367; found 368 (MH^+).

Description 31

3-(4-Bromo-2-trifluoromethoxy)phenyl-8-nitro-sulfanylquinoline (D31)

Prepared from 3-iodo-8-nitroquinoline (D3) and 4-bromo-2-trifluoromethoxythiophenol in an analogous process to that described in Description 26 (D26).

Mass Spectrum : $C_{16}H_8N_2O_3SF_3Br$ requires 444, 446; found [illegible]

Description 32

6-Methyl-8-nitro-3-phenylsulfanylquinoline (D32)

Prepared from 3-bromo-6-methyl-8-nitroquinoline [for synthesis see Tinsley, *J. Am. Chem. Soc.*, 1955, 77, 4175] in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 2.56 (3H, s), 7.38-7.43 (3H, m), 7.47-7.51 (2H, m), 7.63 (1H, s), 7.82 (1H, s), 7.88 (1H, d), 8.78 (1H, d);

Mass Spectrum: $C_{16}H_{12}N_2O_2S$ requires 296; found 297 (MH^+).

Description 33

8-Nitro-3-(3-trifluoromethyl)phenylsulfanylquinoline (D33)

Prepared from 3-iodo-8-nitroquinoline (D3) and 3-trifluoromethylthiophenol in an analogous process to that described in Description 26 (D26).

δ_H ($CDCl_3$) 7.51 (1H, t), 7.59-7.67 (3H, m), 7.74 (1H, br s), 7.94 (1H, dd), 8.03 (1H, dd), 8.13 (1H, d), 8.90 (1H, d);

Mass Spectrum: $C_{16}H_9N_2SO_2F_3$ requires 350; found 351 (MH^+).

Description 34

8-Iodo-(3-trifluoromethyl)phenylsulfonylquinoline (D34)

Prepared from 8-amino-(3-trifluoromethyl)phenylsulfonylquinoline (D17) in an analogous process to that described in Description 6 (D6) in 44% yield;
δ_H ($CDCl_3$) 7.44 (1H, t), 7.71 (1H, t), 7.88 (1H, d), 8.00 (1H, dd), 8.22 (1H, d), 8.29 (1H, br s), 8.52 (1H, dd), 8.1 (1H, d), 9.33 (1H, d);
Mass Spectrum : $C_{16}H_9NO_2SIF_3$ requires 463; found 464 (MH^+).

Example 1
8-(4-Methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1)

A 4:1 mixture of 3-iodo -8-(4-methyl-piperazin-1-yl)-quinoline (D2) and 3-bromo-8-(4-methyl-piperazin-1-yl)-quinoline (D1) (1.5g), phenylsulfinic acid sodium salt, dihydrate (2.52g, 12.6mmol) and copper (I) iodide (2.4g, 12.6mmol) in *N,N*-dimethylformamide (25ml) was stirred in an oil bath at 120°C for 40h under argon. To the reaction mixture, cooled to ambient temperature, was added 5% sodium hydrogen carbonate solution (100ml) and dichloromethane (100ml) with vigorous shaking. The insoluble material was filtered, washed with dichloromethane (3 x 20ml) and discarded. The filtrate and washings were transferred to a separating funnel and the layers separated. The aqueous layer was extracted with dichloromethane (100ml) and the combined organic extracts were washed with water (100ml), dried ($MgSO_4$) and concentrated *in vacuo* to an oil (0.9g). The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane to afford an orange oil (0.28g, Rf 0.11, methanol/dichloromethane 1:19). This material was further purified by passage through a strong cation exchange (SCX) column eluting firstly with methanol (fractions discarded) and then with methanol/aqueous ammonia-880 (10:1) to give the title compound (E1) as an orange [illegible] mmol, 7% over two steps).
δ_H ($CDCl_3$) 2.40 (3H, s), 2.72-2.76 (4H, m), 3.44 (4H, br, s), 7.25-7.27 (1H, m), 7.48-7.61 (5H, m), 7.99-8.02 (2H, m), 8.75 (1H, d, J = 2.4Hz), 9.21 (1H, d, J = 2.4Hz).
Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

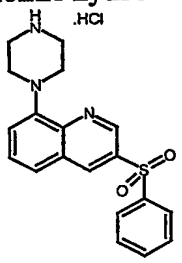
Example 1 (Alternative Procedure)
8-(4-Methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1)

A solution of 8-amino-3-phenylsulfonylquinoline (D5) (38.8 g, 137 mmol) in *t*-butanol (360 ml) was treated with *bis*-(2-chloroethyl)amine hydrochloride (40 g, 138 mmol) and sodium carbonate (72 g, 0.68 mol). The mixture was heated to a vigorous reflux (~100 °C) for 16 h then a further portion of *bis*-(2-chloroethyl)amine hydrochloride (25 g, 86 mmol) introduced and heating continued for a further 4 h. The solution was cooled and a 1:1 mixture of saturated aqueous sodium bicarbonate and aqueous 10% sodium thiosulphate solution (2 L) added. Stirring was continued at ambient temperature for 16 h then the aqueous phase was extracted with dichloromethane (3 x 500 ml), the combined organic phase dried over magnesium sulphate, evaporated *in vacuo* and subjected to chromatography on a Biotage Flash 75 apparatus (1 kg Silica gel) to afford the title compound (E1) as the free base form (11.6 g), identical spectroscopically to that prepared by the first method.
A portion of this material was treated with 1M HCl in ether then evaporated to afford the hydrochloride salt as a yellow solid;

δ_H ($CDCl_3$) 2.95 (3H, d), 2.38-3.52 (4H, m), 4.01-4.06 (2H, m), 4.19-4.26 (2H, m), 7.60 (2H, t), 7.70 (1H, t), 7.96 (1H, t), 8.07 (2H, s), 8.09 (2H, s), 9.34 (1H, d), 9.63 (1H, d), 12.9 (1H, br s)

Example 2

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2)



A stirred solution of 8-(4-methyl-piperazin-1-yl)-3-phenylsulfonylquinoline (E1) (0.148g, 0.4mmol), 1-chloroethyl chloroformate (0.093ml, 0.85mmol) and N,N-diisopropylethylamine (0.148ml, 0.85mmol) in 1,2-dichloroethane (9ml) was heated at reflux for 1.25h under argon. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to an oil. The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane, pooling fractions which contained the major component (Rf 0.9, methanol/dichloromethane 1:19). The purified material was redissolved in methanol (15ml) and the solution was refluxed for 1h under argon. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to a solid which was stirred with diethyl ether (5ml) and filtered to afford the title compound (E2) (0.08g, 0.21mmol, 51%).

δ_H (d_6-DMSO) 3.32 (4H, br s), 3.55 (4H, br s), 7.35 (1H, d, J = 6.5Hz), 7.63-7.77 (4H, m), 7.86 (1H, d, J = 7.4Hz), 8.10 (2H, m), 9.10 (1H, d, J = 2.4Hz), 9.21 (2H, s), 9.24 (1H, d, J = 2.4Hz).

Mass Spectrum : $C_{19}H_{19}N_3O_2S$ requires 353; found 354 (MH^+).

Example 2 (Alternative Procedure)

3-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2)

A mixture of 8-(4-*t*-butoxycarbonyl)piperazin-1-yl-3-phenylsulfonylquinoline (D7) (35.7 g, 78.8 mmol), 1,4-dioxane (200 ml) and 4 M aqueous HCl (200 ml), was stirred at ambient temperature for two hours, then the solvent evaporated. The residue was co-evaporated several times from toluene and the remainder crystallised from hot ethanol to give the title compound (E2) (18.9 g, 68%) as a yellow crystalline solid.

δ_H (d_6-DMSO) 3.32 (4H, br s), 3.55 (4H, br s), 7.35 (1H, d, J = 6.5Hz), 7.63-7.77 (4H, m), 7.86 (1H, d, J = 7.4Hz), 8.10 (2H, m), 9.10 (1H, d, J = 2.4Hz), 9.21 (2H, s), 9.24 (1H, d, J = 2.4Hz).

Mass Spectrum : $C_{19}H_{19}N_3O_2S$ requires 353; found 354 (MH^+).

m.p. 200°C (phase change), 270-274°C (decomposed)

Example 3

3-(2-Chloro)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E3)

bis-(2-Chloro-ethyl)-amine hydrochloride (0.36 g, 1.89 mmol) and sodium carbonate (0.50 g, 4.72 mmol) were added to a suspension of 8-amino-3-(2-chloro)phenylsulfonylquinoline (D10) (0.30 g, 0.94 mmol), in *n*-butanol (10 ml). The stirred suspension was heated at reflux for 48 h. The reaction mixture was cooled to ambient temperature, diluted with dichloromethane (50 ml)

and the solution washed with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to an oil. The oil was purified by chromatography over silica gel eluting with a gradient of methanol/dichloromethane to afford 3-(2-chlorophenylsulfonyl)-8-(4-methylpiperazin-1-yl)quinoline as an oil (0.17 g, 44%). A stirred solution of 3-(2-chlorophenylsulfonyl)-8-(4-methylpiperazin-1-yl)quinoline (0.17 g, 0.42 mmol), 1-chloroethyl chloroformate (0.14 ml, 1.27 mmol) and *N,N*-diisopropylethylamine (0.22 ml, 1.27 mmol) in 1,2-dichloroethane (8 ml) was heated at reflux for 1 h under argon. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to an oil. This material was redissolved in methanol (10 ml) and the solution was refluxed for 1 h under argon. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to a solid which was purified by preparative HPLC. The pure material was stirred with 1 M HCl/diethyl ether (5 ml) and methanol (5 ml), then the resulting mixture was evaporated *in vacuo* to afford the title compound (E3).
δ_H (CD_3OD) 3.31 (4H, br s), 3.53 (4H, br s), 7.57 (1H, d), 7.61 (1H, d), 7.69 (2H, t), 7.75 (1H, t), 7.89 (1H, d), 8.48 (1H, d), 9.10 (1H, s), 9.25 (1H, s).
Mass Spectrum : $C_{19}H_{18}ClN_3O_2S$ requires 387; found 388 (MH^+).

Example 4

3-(3-Chloro)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E4)

Prepared from 8-amino-3-(3-chloro)phenylsulfonylquinoline (D11) in an analogous process to that described in Example 3 (E3).
δ_H (CD_3OD) 3.31 (4H, br s), 3.53 (4H, br s), 7.56-7.64 (2H, m), 7.69-7.76 (2H, m), 7.87 (1H, t), 8.01 (1H, d), 8.13 (1H, s), 9.12 (1H, s), 9.29 (1H, s);
Mass Spectrum : $C_{19}H_{18}ClN_3O_2S$ requires 387, 389; found 388, 390 (MH^+).

Example 5

3-(2-Fluoro)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E5)

Prepared from 8-amino-3-(2-fluoro)phenylsulfonylquinoline (D12) in an analogous process to that described in Example 3 (E3).
δ_H (CD_3OD) 3.51 (4H, br s), 3.59 (4H, br s), 7.30 (1H, t), 7.49 (1H, t), 7.54 (1H, d), 7.72 (2H, t), 7.86 (1H, d), 8.23 (1H, t), 9.05 (1H, s), 9.27 (1H, br s);
Mass Spectrum : $C_{19}H_{18}FN_3O_2S$ requires 371; found 372 (MH^+).

Example 6

3-(4-Chloro)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E6)

Prepared from 8-amino-3-(4-chloro)phenylsulfonylquinoline (D13) in an analogous process to that described in Example 3 (E3).
δ_H (CD_3OD) 3.54-3.57 (8H, br s), 7.63 (2H, d), 7.84 (2H, br s), 8.03-8.06 (1H, m), 8.12 (2H, d), 9.39 (2H, br s).
Mass Spectrum : $C_{19}H_{18}ClN_3O_2S$ requires 387; found 388 (MH^+).

Example 7

3-(3-Fluoro)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E7)

Prepared from 8-amino-3-(3-fluoro)phenylsulfonylquinoline (D14) in an analogous process to that described in Example 3 (E3).

δ_H (CD_3OD) 3.53-3.68 (8H, m), 7.41-7.56 (2H, m), 7.62-7.75 (2H, m), 7.85-7.95 (3H, m), 9.09 (1H, d), 9.27 (1H, d)

Mass Spectrum : $C_{19}H_{18}FN_3O_2S$ requires 371; found 372 (MH^+).

Example 8

3-(4-Bromo-2-trifluoromethoxy)phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E8)

Prepared from 8-amino-3-(4-bromo-2-trifluoromethoxy)phenylsulfonylquinoline (D15) in an analogous process to that described in Example 3 (E3).

δ_H (CD_3OD) 3.54 (4H, m), 3.60 (4H, m), 7.58 (1H, dd), 7.66 (1H, t), 7.74 (1H, t), 7.86 (2H, dd), 8.30 (1H, d), 9.03 (1H, d), 9.23 (1H, d);

Mass Spectrum : $C_{20}H_{17}BrF_3N_3O_3S$ requires 515, 517; found 516, 518 (MH^+).

Example 9

8-Piperazin-1-yl-3-(3-trifluoromethyl)phenylsulfonylquinoline hydrochloride (E9)

To a stirred solution of 8-(4-t-butyloxycarbonyl)piperazin-1-yl-3-(3-trifluoromethyl)phenylsulfonylquinoline hydrochloride (D8) (0.33 g, 0.63 mmol) in dioxane (10 ml) was added 4 M HCl (10 ml). After stirring for 4 h, the solvents were removed *in vacuo* to afford the title compound (E9) as a colourless solid (0.30 g, 97%).

δ_H (CD_3OD) 3.54-3.63 (8H, m), 7.88-8.00 (3H, m), 8.03-15 (2H, m), 8.44 (2H, d), 9.48 (1H, d), 9.56 (1H, d).

Mass Spectrum : $C_{20}H_{18}F_3N_3O_2S$ requires 421; found 422 (MH^+).

Example 10

7-Chloro-3-phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E10)

To a stirred solution of 3-phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E2) (54 mg, 0.14 mmol) in glacial acetic acid (0.5 ml), at room temperature was added *N*-chlorosuccinimide (19 mg, 0.14 mmol). After 16 h the solvent was removed and the mono chlorinated product isolated by preparative reverse phase gradient chromatography (10-90% acetonitrile in water). After removal of the solvents the residue was dissolved in methanol and treated with a solution of hydrogen chloride in diethyl ether (1 M). The solvent was removed to afford the title compound (E10). (9 mg 17%).

δ_H ($CDCl_3$) 3.4 (4H, br.m), 3.6 (4H, v.br m), 7.61 (3H, m), 7.68 (2H, t), 8.05 (2H, d), 8.77 (1H, d), 9.22 (1H, d), 9.74 (2H, br NH2).

Mass Spectrum : $C_{19}H_{18}ClN_3O_2S$ requires 387, 389 ; found 388, 390 (ES+) (MH^+).

Example 11

6-Methyl-3-phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E11)

Prepared from 8-amino-6-methyl-3-phenylsulfonylquinoline (D16) using an analogous process to that described in Example 3 (E3).

δ_H (CD_3OD) 2.51 (3H, s), 3.30 (4H, br s), 3.55 (4H, br s), 7.32 (1H, s), 7.26-7.67 (4H, m), 8.07 (2H, d), 8.88 (1H, d), 9.14 (1H, d);
Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

Example 12

(*R*)-8-(3-Methyl)piperazin-1-yl-3-phenylsulfonylquinoline hydrochloride (E12)

8-Iodo-3-phenylsulfonylquinoline (D6) (200 mg, 0.51 mmol) was dissolved in dry, de-gassed dioxane (4 ml) under argon. To this solution was added sodium *t*-butoxide (68 mg, 0.71 mmol) and (*R*)-(-)-2-methylpiperazine (61 mg, 0.61 mmol) followed by a suspension of catalyst under argon. The catalyst was prepared by sonicating *tris*-(dibenzylideneacetone)dipalladium(0) (14 mg, 0.015 mmol) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (18 mg, 0.015 mmol) in dry degassed dioxane (1 ml) for 2 minutes. This mixture was stirred at 40 °C for 5 h then a further charge of catalyst was administered (prepared as above on half the scale) and stirring continued for 16 h at 40 °C.

The mixture was filtered and the solvent removed. The residue was dissolved in methanol and passed down an SCX ion exchange column eluting with methanol to remove impurities. The product was recovered by eluting with 15% 0.880 aqueous ammonia in methanol. The solvent was removed and the residue dissolved in methanol and treated with a solution of hydrogen chloride in diethyl ether (1 M). The solvent was removed and the residue recrystallised from ethanol to afford the title compound (E12) (40 mg 16%);

δ_H (CD_3OD): 1.40 (3H, d), 2.96 (1H, t), 3.19 (1H, m), 3.51 (2H, m), 3.69 (1H, m), 3.95 (2H, d), 7.46 (1H, d), 7.62-7.70 (4H, m), 7.81 (1H, d), 8.09 (2H, d), 8.99 (1H, d), 9.22 (1H, d);
Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

Example 13

(*S*)-8-(3-Methyl)piperazin-1-yl-3-phenylsulfonylquinoline hydrochloride (E13)

Prepared from (*S*)-(+)-2-methylpiperazine using an analogous process to that described in Example 12 (E12) affording the title compound (E13) (77 mg, 37%) as a yellow solid;
δ_H (CD_3OD): 1.40 (3H, d), 2.96 (1H, t), 3.19 (1H, m), 3.51 (2H, m), 3.69 (1H, m), 3.95 (2H, d), 7.46 (1H, d), 7.62-7.70 (4H, m), 7.81 (1H, d), 8.09 (2H, d), 8.99 (1H, d), 9.22 (1H, d);
Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

Example 14

8-Homopiperazin-1-yl-3-phenylsulfonylquinoline hydrochloride (E14)

Crude 8-(4-*t*-butoxycarbonyl)homopiperazin-1-yl-3-phenylsulfonylquinoline (D9) was dissolved in dioxane (2 ml) plus 4 M hydrochloric acid (2 ml) and stirred at 80 °C for 1 h, when a homogeneous solution had formed. The solvents were removed and the residue dissolved in methanol and passed down an SCX ion exchange column eluting with methanol. The product was recovered by further elution with 15% 0.880 aqueous ammonia in methanol. The solvents were removed and residue treated with a solution of hydrogen chloride in diethyl ether (1M). The solvents were removed and the residue recrystallised from ethanol to afford the title compound (E14) (20 mg, 10%);

δ_H (CD_3OD): 2.31 (2H, m), 3.45 (2H, m), 3.55 (2H, m), 3.74 (4H, m), 7.40 (1H, d), 7.60-7.70 (5H, m), 8.08 (2H, m), 8.94 (1H, d), 9.18 (1H, d);
Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

Example 15

8-((*S*)-2-Methyl-piperazin-1-yl)-3-phenylsulfonyl-quinoline hydrochloride (E15)

(*S*)-3-Methyl-4-(3-phenylsulfonyl-quinolin-8-yl)-piperazine-1-carboxylic acid *tert*-butyl ester was prepared in accordance with the procedure described in Description 7 (D7) by replacing piperazine-1-carboxylic acid *tert*-butyl ester with (S)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester. The resultant compound was then treated to the conditions described in Example 2 (E2) to afford the title compound (E15).

δ_H (CD_3OD): 0.92 (3H, d), 3.25 (1H, m), 3.43 (3H, m), 3.57 (2H, m), 4.09 (1H, br s), 7.64 (2H, t), 7.71 (1H, t), 7.90 (1H, t), 7.98 (1H, d), 8.14 (3H, m), 9.38 (1H, s), 9.39 (1H, s);
Mass spectrum: $C_{20}H_{21}N_3O_2S$ requires 367; found 368 (MH^+).

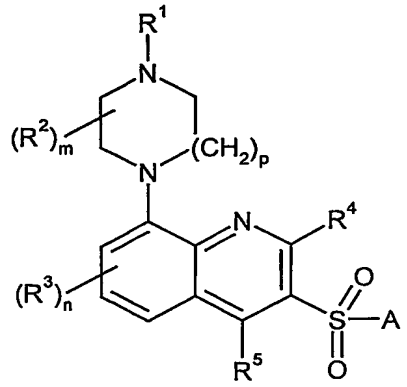
Pharmacological data

Compounds can be tested following the procedures outlined in WO98/27081.

The compounds of Examples E1-E2 were tested and showed good affinity for the 5-HT_6 receptor, having pKi values > 8.0 at human cloned 5-HT_6 receptors. The compounds of examples E3 – E15 were also tested and showed good affinity for the 5-HT_6 receptor, having pKi values > 7.5 at human cloned 5-HT_6 receptors.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl or R^1 is linked to R^2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$;

R^3, R^4 and R^5 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^6R^7$;

R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

m represents an integer from 1 to 4, when m is an integer greater than 1, two R^2 groups may instead be linked to form a group CH_2, $(CH_2)_2$ or $(CH_2)_3$;

n represents an integer from 1 to 3;

p represents 1 or 2;

A represents a group $-Ar^1$ or $-Ar^2Ar^3$;

Ar^1, Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^8R^9$ or $SO_2NR^8R^9$, wherein R^8 and R^9 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

or solvates thereof.

2. A compound according to claim 1 which is a compound of formula E1-E15 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of depression, anxiety, obesity and cognitive memory disorders.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.